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10/576,274	10/09/2007	Rehab Al-Jamal	MUR-06-1101	9435

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/576,274	AL-JAMAL ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,16,20-24,26,27 and 31-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,16,20-24,26,27 and 31-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/21/2010 and 09/21/2010 and 12/28/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/21/2010 has been entered.

2. Claims 1, 16, 20-24, 26, 27, 31-35 are pending and under examination in the instant application.

3. Applicant's IDS, filed 09/21/2010 and 12/28/2010, is acknowledged.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 16, 20-24, 26, 27, 31-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record.

Applicant's arguments, filed 09/21/2010, have been fully considered, but have not been found convincing.

Applicant points to Dr. Al-Jamal declaration under 1.132, filed 09/21/2010, to support that anti-TAEKLK antibodies lead to modulation in the MMP balance. Applicant points that the declaration includes experimental data showing that targeting the TAEKLK amino acid residues of beta-1 integrin using the JB1a antibody had an effect on MMP12 levels in emphysematous mice and also had an effect on MMP2, 9 and 12 levels in emphysematous adult human lung fibroblasts.

However, Dr. Al-Jamal's declaration under 1.132, filed on 09/21/2010, is insufficient to overcome the rejection for the following reasons: (a) The declaration is limited in scope to the anti-b1 antibody, JB1a, emphysematous mice, inhibiting MMP12, and in vitro inhibiting MMP2/9 at 2 and 6 hrs (act on type IV collagen), while increase at 4hrs. However, the claims are drawn to a method of promoting tissue repair with anti-TAEKLK antibodies which results in an alteration in the metalloproteinase balance, wherein the alteration in the metalloproteinase

balance results in at least one of (i) an increase in inactive MMP9, and (ii) a decrease in MMP1 in addition to an increase in TIMP1 in vivo. The declaration fails to show the effect of the JB1a antibody on MMP-1, MMP-7, MMP-14, MMP-15, MMP-16, MMP-26 among others. It is not clear whether the effect of JB1a is selective to MMP-12, MMP2/9 in PPE-induced emphysema or would act on altering all the metalloproteinases in all tissue repair including emphysema. There are no reports regarding in vivo protection against emphysema by selective MMP-12 inhibitors at the time the invention was made (see Ma et al, J. Med. Chem. 2006, 49, 456-458).

Applicant asserts that SG/7, SG/19, C30B and D11B antibodies bind to TAEKLK sequence of beta 1 integrin. Applicant further points that SG/19 effect the activity of MMP9 (Saito 2010 and Tsuji 2002). Applicant concluded that the effect of anti-TAEKLK antibodies on modulation of MMP balance has been shown.

However, applicant fails to show the effect of MMP9 on any tissue repair. Tsuji et al demonstrated that laminin-5 potentiates the production of MMP-9 by A375 melanoma cell (tumor cells). Saito teaches the potentiation of cell invasion and matrix metalloproteinase production by $\alpha 3\beta 1$ integrin-mediated adhesion of gastric carcinoma cells to laminin-5. In the contrary, Applicant argues under art rejections that the invention does not encompass malignant transformation. Applicant argues that on page 10 of the remarks that tumor cells do not constitute cells wherein extracellular matrix has been degraded. In any way, MMP-9/laminin-5 does not represent the claimed alteration in the metalloproteinase balance in the genus of tissue repair.

Applicant submits that as would be known to those skilled in the art, raising another clone to the TAEKLK sequence of beta 1integrin will replicate the observed effects of JB1a binding and result in modulation of the MMP balance and tissue repair. In providing the sequence of beta 1 integrin to which the antibody must bind in order to achieve the modulation of the MMP balance and tissue repair.

Contrary to Applicant assertion, JB1a antibody is conformational antibody. The current state of the art in epitope structure prediction is limited given the noncontiguous amino acid residues constitute conformational epitopes, and that the dynamics of binding is often not integrated into the epitope prediction equation, making epitope structure prediction a complex four-dimensional problem. Applicant's predictions concern only continuous epitopes and it is unrealistic to reduce the complexity of epitopes that always possess conformational features to one-dimensional, liner peptide models.

Applicant points that the epitope of SG/19 antibody was reported in 2004 (Luo et al) showing that clone SG/19 induces an intermediate conformational state of beta 1 integrin similar to that induced by JB1a, as evidenced by the inventor's FRET data for JB1a submitted in the response dated 7/28/2009.

However, JB1a binds 82-87 and possible 179–184. However, SG/19 binds only 82-87 (see Al-Jamal, Pharmacology & Therapeutics 120 (2008) 81–101). Further, SG/19 clone has not been shown to promote any tissue repair via the inhibition of the apoptotic pathway, alteration in the metalloproteinase balance and increase in the anabolism of the extracellular matrix. Inhibition of MMP9-laminin-5 with SG/19 alone does not meet the other anti-TAEKLK antibodies requirements including the inhibition of the apoptotic pathway and an increase in the anabolism of the extracellular matrix. That is the outcome does not only depend on level of MMP9 as required by instant claim 1, it is the combination of all three requirements (i-iii) would lead to the promotion of the tissue repair.

6. Claims 1, 16, 20-24, 26, 27, 31-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting tissue repair in lung emphysema comprising administering the monoclonal antibody produced by commercial clone JB1a or antibodies that binds TAEJKJ of SEQ ID NO:1, does not reasonably provide enablement for methods claimed in claims 1, 16, 20-24, 26, 27, 31-35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons of record.

Furthermore, regarding in vivo methods which rely on generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

Further, in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

At issue is whether or not the claimed anti-TAEKLK antibodies, which modulate the function of β1 integrin would function to promote any tissue repair including skin tissue, tissue of the central nervous system, liver tissue, kidney tissue, tissue of the cardiovascular system, bone tissue and

cartilage. However, in order for this therapy to be predictable, β1 integrin modulation must play a role in all tissue repairs. However, Grose et al (IDS reference AR) in Development 129:2303-2315 (2002) teach that their results reveal a strongly impaired migratory capacity of β1-deficient Keratinocytes in vitro and a dramatic delay in epithelial migration during wound repair in K5β1-null mice. Grose et al present the first in vivo evidence in support of findings from in vitro studies that have shown β1 integrins to be key players in cell migration. However, their results also demonstrate that keratinocytes are not totally dependent on this integrin subunit to heal their wounds. Rather, other integrins appear to compensate at least partially for the lack of β1, leading to complete, although imperfect, re-epithelialisation (page 2314, last ¶). Grose et al teach that keratinocytes proliferation rate in the β1 null keratinocytes was not reduced in early wounds and even increased in late wounds (abstract). Importantly, Grose et al teach that β1-deficient epidermis did cover the wound bed, but the epithelial architecture was abnormal. Zweers et al in J. Invest. Dermatol. 127:467-479, 2007, teaches that integrin α2β1 is required for regulation of murine wound angiogenesis but is dispensable for reepithelialization. Zweers et al teach that reepithelialization of excisional wounds of α2β1-null mice was not impaired, indicating that keratinocytes do not require adhesion to or migration on collagen for wound closure (see abstract). Applicant has no working examples demonstrating an in vivo treatment regiment with anti-β1 antibodies to promote any tissue repair, and the state of the art taught the "β1-deficient animals", α2β1 integrin, is dispensable for reepithelialization. Further, the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed method for promoting tissue repair using anti-β1 antibodies with a reasonable expectation of success. One skill in the art would concluded that a strategy of administering ant-β1 antibody in dermal tissue would require further understanding of the role of anti-β1 in re-epithelializtion.

It is not clear that PPE-induced emphysema would represent all claimed tissue repair including skin tissue, tissue of the central nervous system, liver tissue, kidney tissue, tissue of the cardiovascular system, bone tissue and cartilage. There must be a rigorous correlation of pharmacological activity between the disclosed utility and an in vivo utility to establish practical utility.

If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied. The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements...However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims." MPEP § 2164.03.

"Substantiating evidence may be in the form of animal tests which constitute recognized screening procedures with clear relevance to utility in humans. See Ex parte Krepelka, 231

USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein." Ex parte Maas, 9 USPQ2d 1746

Applicant's arguments, filed 09/21/2010, have been fully considered, but have not been found convincing.

Applicant submits that it is an alteration in MMP balance which results in tissue repair in the Applicants' method rather than the inhibition and/or activation of one or more specific MMPs. An increase in the activity of any given MMP does not decide the outcome as the outcome will also depend on, for example, the level of inhibitors present, the levels of other MMPs which could be activated by the first MMP and which could, in turn, activate other MMPs, and further, the timing of activation of the MMP. Applicant submits that Corey et al, focused on a single MMP9 in transgenically altered animals. There was no description of the effect of genetic deletion of MMP9 on other MMPs or indeed on inhibitors of MMPs (TIMPs).

However, the anti-TAEKLK antibodies are claimed to increase in inactive MMP9 and decrease in MMP1, and further an increase in TIMP1. Now Applicant provides a declaration to included MMP12 and MMP2/9 alteration. It is not clear why the anti-TAEKLK antibodies would act differently from one tissue type compared to another tissue type. Are anti-TAEKLK antibodies selective to specific MMPs or generic to all MMPs? Do the anti-TAEKLK antibodies act as inhibitor and activator of MMPs in concert with the type of tissue repair so that the balance of the inhibition/activation of one MMP or all MMPs counts? The lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims, the claims are not enabled.

Legal Standard for Anticipation/Inherency Under - 35 USC § 102

To anticipate a claim under 35 U.S.C. § 102, a single prior art reference must place the invention in the public's possession by disclosing each and every element of the claimed invention in a manner sufficient to enable one skilled in the art to practice the invention. Scripps Clinic & Research Foundation v. Genetech, Inc., 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1001 (Fed. Cir. 1991); In re Donahue, 766 F2d531, 533, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985). To anticipate, the prior art must either expressly or inherently disclose every limitation of the claimed invention. MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365, 52 U.S.P.Q.2d 1303, 1303 (Fed. Cir. 1999) (citing to In re Schreiber, 128 F.3d 1473, 1477, 44 U.S.P.Q. 1429, 1431 (Fed. Cir. 1997)); Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943, 1946 (Fed. Cir. 1999). To inherently anticipate, the prior art must necessarily

function in accordance with, or include, the claimed limitations. MEHL/Biophile, 192 F.3d at 1365, 52 U.S.P.Q.2d at 1303. However, it is not required that those of ordinary skill in the art recognize the inherent characteristics or the function of the prior art. Id. Specifically, discovery of the mechanism underlying a known process does not make it patentable. See also MPEP §§ 2112, 2112.02 and 2145(II).

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 4, 15-16, 20-25, 28-30 stand and newly addad claim 35 is rejected under 35 U.S.C. 102(b) as being anticipated by US20030109435, as is evidenced by Al-Jamal's declaration, filed 12/28/2009 and Chemicon International catalog no. MAB1965, 9/23/09 (submitted by Applicant on 06/03/2009).

The `435 publication claims a method of inhibiting formation of an amyloid deposit comprising administering an effective dosage of one or more agents that bind to β1under conditions such that the one or more agents inhibit the formation of an amyloid deposit (see published claims 1 4, 14, 21, 50, 53, 70), wherein the agent is an antibody that recognizes the same epitope as an antibody MAV 1965 (claimed clone JB1a) (see published claims 22-39, 71-88), wherein the disease is Alzheimer's disease (see published claims 41, 90) or Parkinson's disease (see published claims 43, 92). The `435 publication teaches that because the meshwork resembled an extracellular matrix, like those formed by integrin, it was investigated whether integrin was present in the HCC; and if so, if integrin facilitated the Aβ meshwork formation on HCC. Gel electrophoresis showed that β1 integrin is expressed in HCC. It was also found that β1 integrin blocking antibodies, including MAB1965 (claimed commercial clone JB1a), could block the Aβ meshwork pattern from forming on HCC (compare FIG. 2A (without antibody) to FIG. 2B (with antibody)). Whether the meshwork pattern was necessary for the toxicity generated by Aβ in these cultures was also investigated. To test this, HCC were incubated with β1 integrin blocking antibodies (AIIB2 (epitope 207-218) and MAB 1965 (epitope 82-87) that had been shown to block the Aβ meshwork. These antibodies also blocked Aβ induced toxicity in a dose dependent manner (FIG. 2C). The antibody AIIB2 is a very potent blocker of Aβ toxicity, exhibiting an IC50 of 170 ng/ml or 1 nM. In contrast, a control antibody had no effect on toxicity (see page 18, example 2).
As is evidenced by Al-Jamal's declaration under ¶5, that administration of JB1a promoted tissue repair in a mouse model of Parkinson's disease.

Catalog No. MAB1965 is the claimed clone JB1a as is evidenced by Chemicon International catalog no. MAB1965.

Although the `435 publication is silent with regard to the JB1a results in (i) inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance and (iii) an increase in the anabolism of the extracellular matrix claimed in claim 1; causes shedding of the beta 1 integrin claimed in claim 34, results in at least one of (i) an increase in inactive MMP9, and (ii) a decrease in MMP1 claimed in claim 23, and further includes an increase in TIMP1 claimed in claim 24, it is noted that a compound and all of its properties are inseparable; they are one and the same thing (see In re Papesch, CCPA 137 USPQ 43; In re Swinehart and Sfiligoj, 169) USPQ 226 (CCPA 1971)). Therefore, in the absence of evidence to the contrary, the JB1a administered would be expected to result in the claimed properties.

It is noted that the CAFC held in Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc., 58 USPQ2d 1508 (CA FC 2001) that when a claimed process is not directed to a new use, consists of the same steps described in a prior art reference, and the newly discovered results of the known process directed to the same purpose are inherent, the process is not patentable.

The reference anticipates the claimed invention.

Applicant's arguments, filed 09/21/2010, have been fully considered, but have not been found convincing

Applicant submits that the `435 fails to teach all of the elements of claim 1 as amended. Specifically, it does not teach administration of an antibody, which binds to the beta 1 integrin molecule in a region of amino acid residues 82-87, to a tissue wherein extracellular matrix of the tissue has been degraded. Paragraph 16 of the `435 states that the invention provides methods of inhibiting formation of an amyloid deposit. ¶199 states that antibodies to the beta 1 integrin subunit inhibit formation of extracellular meshworks of amyloid proteins. Applicant concluded that the `435 clearly teaches that the antibody is administered before degradation of the extracellular matrix in order to inhibit fibril formation. This differs from the claimed method of the present application wherein the antibody is administered following degradation of the extracellular matrix in order to promote tissue repair (emphasis added by Applicant). Applicant submit that the protective effect observed on administration of the antibody in the `435 was not because of inhibition of interaction with degraded extracellular matrix, but rather inhibition of extracellular fibril formation. In ¶312 of the `435 publication, it is taught that fibronectin and meshwarked fibronectin both protected from amyloid toxicity. This indicated that matrix degradation was not the mode for the inhibition of toxicity. This is even more evident by the lack of protective effect reported in the `435 when using laminin in its native form, though antibodies against laminin itself did protect from injury.

However, it appears that applicant and the examiner differ on interpretation of both the claimed methods and the prior art. Also, applicant relies upon an asserted and claimed mechanism of action but does not provide objective evidence that the prior art teaching of treating the same

Alzheimer's disease, or Parkinson's disease patient populations with the same compositions to achieve the same therapeutic effect differs from the claimed methods. The JB1a antibody is used to treat Alzheimer's disease, or Parkinson's disease, not to prevent those diseases. Accordingly, the extracellular matrix of the tissue must have been degraded in those patients. As is evidenced by A1-Jamal's declaration under ¶5, that administration of JB 1 a promoted tissue repair in a mouse model of Parkinson's disease.

8. Claims 1, 16, 21-24 stand and newly added claim 35 is rejected under 35 U.S.C. 102(b) as being anticipated by US. Pat. 6,123,941.

The `941 patent teaches and claims methods for reversing malignant phenotype in tissue by administering an effective amount of an β1 integrin function-blocking antibody or a peptide inhibitor of integrin function to the β1 integrin receptors of tissue in need of such treatment (see patented claim 1), wherein the tissue is a tissue expressing β1 integrin receptors (see patented claim 7), wherein the tissue is selected from the group consisting of breast carcinoma tissue, prostate carcinoma tissue, intestinal tissue, or epithelial tissue (see patented claim 8 wherein the beta 1 integrin function-blocking antibody is a mouse monoclonal JB1a (also referred to as J10: CHIEMICON catalogue #1965) and an antigen binding fragment of monoclonal JB1a (see patented claim 9).

FIG. 9 shows the TUNEL labeling index of day 10-12, bar C shows T-4 tumor cells treated with β1 integrin function-blocking antibody. Non-malignant MEC cells (bar A) respond to an exogenous basement membrane by inhibiting basal apoptosis as evidenced by an apoptotic index of less than 2%. In contrast tumor cells treated with nonspecific Ab (bar B) do not respond appropriately to cues from the ECM and exhibit elevated basal apoptosis rates of greater than 20-30%. Treatment of tumor cells with β1 integrin function-blocking antibody resulted in a significant reduction in basal apoptosis rates of less than 15% suggesting the treatment permitted the tumor cells to respond appropriately to the exogenous basement membrane microenvironment (see col., 13, lines 28-45).

When claim 1 is given its broadest reasonable interpretation: promoting tissue repair can include reversing malignant phenotype in tissue as a result of an inhibition of the apoptotic pathway. The Examiner direct Applicant's attention to the instant specification on page 15, lines 2-21.

Although the `435 publication is silent with regard to the JB1a results in (i) inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance and (iii) an increase in the anabolism of the extracellular matrix claimed in claim 1; causes shedding of the beta 1 integrin claimed in claim 34, results in at least one of (i) an increase in inactive MMP9, and (ii) a decrease in MMP1 claimed in claim 23, and further includes an increase in TIMP1 claimed in claim 24, it is noted that a compound and all of its properties are inseparable; they are one and the same thing (see In re Papesch, CCPA 137 USPQ 43; In re Swinehart and Sfiligoj, 169) USPQ 226 (CCPA 1971)). Therefore, in the absence of evidence to the contrary, the JB1a administered would be expected to result in the claimed properties.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 09/21/2010, have been fully considered, but have not been found convincing.

Applicant submits that that `941 fails to teach all of the elements of claim 1. Specifically, it does not disclose administering an antibody to a tissue wherein extracellular matrix of the tissue has been degraded. Applicant submits that the `941 teaches administering an antibody to tumor cells. The Applicants submit that tumor cells do not constitute cells wherein extracellular matrix has been degraded. Applicant submits that there is a clear difference between tissue wherein extracellular matrix of the tissue has been degraded leading to cell death and tumor tissues wherein synthesis of extracellular matrix is increased and cell death is evaded.

Contrary to Applicant's assertions, the `941 claims a method for reversing malignant phenotype in tissue by administering an effective amount of an β1 integrin function-blocking antibody such as JB1a antibodies. The malignant phenotype can spread by invasion and metastasis which involve de-adhesion of metastatic cells from tumor cell mass, extracellular matrix remodeling and intravasation of tumor cells to the blood. The use of the JB1a to reverse extracellular matrix remodeling reads on the claimed method of promoting tissue repair. Malignant phenotype indicates that the tumor cells degraded the extracellular matrix via MMPs and/or cathapsins. Accordingly, prior art method reads on the claimed invention.

Applicant submits that the `941 patent teaches administration of the antibody to reverse the malignant phenotype in cells, thus reducing cell division and reinstituting the normal cell cycle wherein the cells can die naturally. In the Applicant's claimed method, administration of the antibody results in an inhibition of the apoptotic pathway, thus preventing cell death during degenerative injury wherein the cells would otherwise die.

However, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which a particular antibody to promote tissue repair does not appear to distinguish the prior art teaching the same methods to achieve the same end results. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Applicant submits that the statement that the `941 T4 cells revert to normal phenotype when beta 1 integrin function-blocking antibody is applied, but normal cells Die as a result of application of the bet 1 integrin function-blocking antibody and the level of response varies as a function of the concentration of applied antibody such as that it is important to use the correct concentration to balance these two effects. The Applicants submit that to those skilled in pharmacology, this statement regarding the dependency of the pro-apoptotic effect on dose indicates that saturation

of binding sites with the antibody was incomplete. Dosage is usually determined by the number of binding sites. In tumors, there have been recent reports where the level of beta1 integrin is increased in addition to its glycosylation. Therefore, it would be clear to those skilled in the art that the doses used in the `941 would be relatively higher than those used in normal non-transformed tissue.

However, Applicant's claims are not drawn to any specific dosage. Applicant argues limitations that are not claimed. Further, a patent shall be presumed valid (35 U.S.C. 282) until declared invalid in a court of competent jurisdiction, and that presumption includes the presumption of operability (Metropolitan Eng. Co. v. Coe, 78 F.2d 199, 25 USPQ 216 (D.C.Cir. 1935). The challenger of a patent's validity bears the burden of proving invalidity by clear and convincing evidence.

Applicant points that beta1 integrin in normal cells is known to induce detachment-induced cell death or anoikis (a form of apoptosis). The Applicants' claimed method does not related to inhibition of the beta 1 integrin antibody as the more potent inhibitor clone 6S6 failed to produce similar effects to those shown by JB1a. Thus, inhibition of beta 1 integrin is not sufficient to explain the effects presented in Table III of US `941 wherein the efficacy of JB1a is statistically significant from that disclosed from targeting using clone AIIB2 in a comparable ascites formaulation (based on the disclosed mean and SEM assuming the values are from at least 3 independent measures. AIIB2 is known to those skilled in the art as a potent inhibitor similar to clone 6S6.

The Examiner is not clear why Applicant is arguing the difference between AIIB2 and JB1a. It is noted that the `941 patent claims using JB1a antibody in patented claim 9 in a method for reversing malignant phenotype in tissue which reads on the claimed invention. It is noted that the CAFC held in Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc., 58 USPQ2d 1508 (CA FC 2001) that when a claimed process is not directed to a new use, consists of the same steps described in a prior art reference, and the newly discovered results of the known process directed to the same purpose are inherent, the process is not patentable.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over US. Pat. 6,123,941 as in view of Owens et al (1994) for the reasons of records.

Applicant's arguments, filed 09/21/2010, have been fully considered, but have not been found convincing.

Applicant submits that Owens et al does not remedy the `941 patent deficiencies.

However, it remains the Examiner's position that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by US. Pat. 6,123,941 as chimeric, humanized antibody taught by the Owens et al. because the humanized antibodies are much less likely to induce an immune response and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens et al.

11. Claims 1, 16, 20-24, 31 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 20070048321, in view of Chen et al, (J. Biol. Chem. 276(13):10443–10452, 2001).

The `321 publication teaches and claims a method for treating fibrosis in a subject with a fibrotic condition, comprising administering to a patient a pharmaceutical composition, the pharmaceutical composition comprising an effective amount of an antibody molecule comprising antigen binding regions derived from the light and heavy chain variable regions of an antibody to an integrin and fragment thereof (see published claim 1), wherein the fibrotic condition is liver, lung, kidney, heart blood vessels, gastrointestinal tract which occurs in disorders such as pulmonary fibrosis, myelofibrosis, liver cirrhosis, mesangial proliferative glomerulonephritis, crescentic glomerulonephritis, diabetic nephropathy, renal interstitial fibrosis, renal fibrosis in patients receiving cyclosporin, and HIV associated nephropathy (see ¶33). The publication further teaches inhibiting overproduction of scarring in patients who are known to form keloids or hypertrophic scars, inhibiting or preventing scarring or overproduction of scarring during healing of various types of wounds including surgical incisions, surgical abdominal wounds and traumatic lacerations, preventing or inhibiting scarring and reclosing of arteries following coronary angioplasty, preventing or inhibiting excess scar or fibrous tissue formation associated with cardiac fibrosis after infarction and in hypersensitive vasculopathy (see ¶37), wherein the antibody is selected from the group consisting essentially of an anti-$\alpha 1\beta 1$ antibody, anti- $\alpha 2\beta 1$ antibody, and anti- $\alpha 6\beta 1$ antibody (see published claim 2), wherein the antibody is an anti-β antibody (see published claim 3) such as anti-$\beta 1$ (see ¶21), wherein the fibrotic condition is pulmonary fibrosis (see published claim 8), wherein the antibody is selected from the group consisting of a human antibody, a chimeric antibody, a humanized antibody and fragments

thereof (see published claim 9). The `321 publication teaches that collagen is a fibril-forming protein which is essential for maintaining the integrity of the extracellular matrix found in connective tissues. The production of collagen is a highly regulated process, and its disturbance may lead to the development of tissue fibrosis. While the formation of fibrous tissue is part of the normal beneficial process of healing after injury, in some circumstances there is an abnormal accumulation of fibrous materials such that it may ultimately lead to organ. Injury to any organ leads to a stereotypical physiological response: platelet-induced hemostasis, followed by an influx of inflammatory cells and activated fibroblasts. Cytokines derived from these cell types drive the formation of new extracellular matrix and blood vessels (granulation tissue). The generation of granulation tissue is a carefully orchestrated program in which the expression of protease inhibitors and extracellular matrix proteins is upregulated, and the expression of proteases is reduced, leading to the accumulation of extracellular matrix (see ¶3). The major cell surface collagen receptors are the αlβ1 (VLA-1) and α2β1 (VLA-2) integrins. Both integrins have been implicated in cell adhesion and migration on collagen; in promoting contraction of collagen matrices, and in regulating the expression of genes involved in the remodeling of the extracellular matrix. For example, when fibroblasts contact a collagen matrix, signaling through the αlβ1 integrin down-regulates collagen I expression, while signaling through α2β1 up-regulates the expression of matrix metalloproteases. The `321 publication teaches that our data demonstrated that treatment with anti-α1β1 or anti-α2β1 antibody reduced BL-induced lung collagen accumulation in mice. However, treatment with either antibody did not affect BL-induced increases in the BAL cell number and protein level, except for anti α2β1 which reduced the total BAL cells. It is concluded that integrins α1β1 and α2β1 play important roles in BL-induced pulmonary fibrosis and the use of anti α1β1 or anti α2β1 antibody has great antifibrotic potential in vivo (see ¶84).

The `321 publication does not teach an antibody that binds to the beta1 integrin molecule in a region of amino acid residues 82-87 comprising residues TAEKLK in claim 1, wherein the antibody is JB1a in claims 16.

However, Chen et al teach the functional-blocking mAbs against various integrins including anti-β1 antibody, JB1a (see page 10444, under antibodies). Chen et al teach the mAb against the integrin β1 subunit strongly inhibited cell adhesion to CTGF (Fig. 2D). Similar inhibitory effect was observed in adhesion to type I collagen, a known substrate for β1 integrins (see 10445, 2nd col., 3rd ¶).

Those of skill in the art would have had reason to use the functional-blocking anti-β1 antibody, JB1a of Chen article as a substitute for the treatment taught `321 publication because, like the compounds taught in `321 publication, anti-β1 antibodies inhibit α1β1 or α2β1 ligands, collagen I and IV (see Fig. 1 and 2 of the `321 publication). Functional-blocking antibodies to either of the α1, α2 or β1 would have inhibited the α2β1 ligands interaction. This is pharmaceutical version of the two for the price of one. That is by targeting β1 with JB1a antibody, both α1β1

and α2β1 are inhibited. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

Although the combined reference teachings is silent with regard to the JB1a results in (i) inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance and (iii) an increase in the anabolism of the extracellular matrix claimed in claim 1; causes shedding of the beta 1 integrin claimed in claim 34, results in at least one of (i) an increase in inactive MMP9, and (ii) a decrease in MMP1 claimed in claim 23, and further includes an increase in TIMP1 claimed in claim 24, it is noted that a compound and all of its properties are inseparable; they are one and the same thing (see In re Papesch, CCPA 137 USPQ 43; In re Swinehart and Sfiligoj, 169) USPQ 226 (CCPA 1971)). Therefore, in the absence of evidence to the contrary, the JB1a administered would be expected to result in the claimed properties.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claims 1, 16, 20-24 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over US. Pat. 6,251,419, in view of Weigel-Kelley et al (Blood. 2003;102:3927-3933, Epub 2003 Aug 7).

The `419 patent teaches and claims a method for controlling tissue regeneration of the periodontium comprising applying to the periodontium a membrane comprising a resorbable polymer membrane comprising: (a) a first antibody, which binds to an α chain; and (b) a second antibody which binds to an integrin β chain; wherein either the first antibody binds to the α-6 subunit and/or the second antibody binds to the β-1 subunit (see patented claim 11). The `419 patent teaches examples are monoclonal mouse antibodies against the integrin subunit α6 (clone GoH3; Dianova, Hamburg), and integrin subunit β-1 (clone P4c10; Biomol, Hamburg). In particular, monoclonal antibodies directed against the integrin subunits α-6 and β-1 are suitable, separately and as a mixture (see col., 1 line 64 to col., 2, line 4). The `419 patent teaches that in epithelial wound healing, particularly the integrin subunits α-6 and β-1 serve for connecting the keratocytes migrating into the wound region with all extracellular matrix proteins of the basal membrane. The invention is now based on the fact that growth inhibition of the epithelium and growth stimulation shall simultaneously take place in the connective tissue. This serves for supporting regeneration of the functional periodontium and accelerated wound healing (see col. 2 lines 26-34).

The claimed invention differs from the reference teachings only by the recitation of anti-TAEKLK antibody in claim 1, JB1a in claims 16 and 21.

However, Weigel-Kelley et al tested whether α5β1 integrins were involved in the adhesion-dependent permissiveness of K562 cells for parvovirus B19 internalization, Weigel-Kelley et al incubated PMA-treated K562 cells in the presence of divalent ions and β1 integrin function-blocking (or high-affinity conformation-destabilizing; P4C10, JB1a) antibodies, revealed a reduction in nuclear localization of Cy3-labeled parvovirus B19 particles by β1 integrin function-blocking antibodies (P4C10) 30 minutes after infection (Figure 2Ai-Aii) (see page 3929, 1st col., 1st full ¶). Further, transduction of PMA-treated K562 cells with recombinant parvovirus B19-Luc vectors was inhibited by inhibitory β1 integrin antibodies (JB1a) (see Fib. 2b).

Those of skill in the art would have had reason to use the functional-blocking anti-β1 antibody, JB1a of Weigel-Kelley et al article as a substitute for the treatment taught `419 patent because, like the compounds taught in `419 patent, anti-β1 antibody, JB1a is β1 integrin function-blocking or high-affinity conformation-destabilizing antibody (see Weigel-Kelley et al). Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421. A person of ordinary skill in the art would have recognized the interchangeability of the element shown in the prior art for the corresponding element recited in the claim. Caterpillar Inc. v. Deere & Co., 224 F.3d 1374, 56 USPQ2d 1305 (Fed. Cir. 2000); Al-Site Corp. v. VSI Int' l, Inc., 174 F.3d 1308, 1316, 50 USPQ2d 1161, 1165 (Fed. Cir. 1999); Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus. Inc., 145 F.3d 1303, 1309, 46 USPQ2d 1752, 1757 (Fed. Cir. 1998); Lockheed Aircraft Corp. v. United States, 193 USPQ 449, 461 (Ct. Cl. 1977); Data Line Corp. v. Micro Technologies, Inc., 813 F.2d 1196, 1 USPQ2d 2052 (Fed. Cir. 1987).

Although the combined reference teachings is silent with regard to the JB1a results in (i) inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance and (iii) an increase in the anabolism of the extracellular matrix claimed in claim 1; causes shedding of the beta 1 integrin claimed in claim 34, results in at least one of (i) an increase in inactive MMP9, and (ii) a decrease in MMP1 claimed in claim 23, and further includes an increase in TIMP1 claimed in claim 24, it is noted that a compound and all of its properties are inseparable; they are one and the same thing (see In re Papesch, CCPA 137 USPQ 43; In re Swinehart and Sfiligoj, 169) USPQ 226 (CCPA 1971)). Therefore, in the absence of evidence to the contrary, the JB1a administered would be expected to result in the claimed properties.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1, 16 and 20-24, 27 and 31-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 11, 16, 19, 24, 25, 32, 35, 57 and 59-63 of copending Application No. 12528749. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are using the same antibody clone JB1a that binds amino acid residues 82-84 and possible 179-184 (as is evidenced by Al-Jamal and Harrison, Pharmacology & Therapeutics 120 (2008) 81-101, see Table 1) to teat tissue damage.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant submits that because the rejection is provisional, they will address it when the rejection becomes non-provisional.

However, the rejection is maintained until it is addressed.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 29, 2010

/Maher M. Haddad/
Primary Examiner,
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